specifically when considering radium-223[59] and lutetium-177-prostate-specific membrane antigen.[60] However, the use of radiopharmaceutical therapy for endpoints aside from pain response at the site of index (irradiated) bone metastases is beyond the scope of this guideline.[55-59,61-63]

Palliative RT and bisphosphonate therapy

Bone modifying agents such as bisphosphonate therapies do not obviate the routine need for palliative RT for patients with localized painful bone metastases. The task force reviewed a variety of RCTs and nonrandomized studies, including those comparing bisphosphonates with RT directly and those comparing combined RT and bisphosphonates with RT alone.[64-67] A UK trial (n = 470) randomized patients with metastatic prostate cancer to local conventional palliative RT (800 cGy in 1 fraction) or a single 6 mg infusion of ibandronate and found no difference in overall pain response at 4 or 12 weeks; however, a more rapid initial response with RT was observed.[64]

Palliative RT and kyphoplasty, vertebroplasty, cryoablation, hyperthermia, and radiofrequency ablation

Although data are limited, none of the available evidence suggests that local interventional treatments—including kyphoplasty, vertebroplasty, cryoablation, radiofrequency ablation, or hyperthermia—obviate the need for RT for patients with localized symptomatic bone metastases.[68,69] Multidisciplinary discussion, inclusive of interventional radiology, is encouraged to identify patients for whom these local interventions should be considered, alone or in combination with palliative RT.

KQ3: Dose fractionation, dose constraints, and techniques for initial palliative treatment (Table 5)

In adult patients with symptomatic bone metastases, what RT dose-fractionation regimens, dose constraints, and techniques are appropriate for the initial palliative treatment of bone metastases?

Although the role of RT in the treatment of symptomatic bone metastases is widely accepted, the optimal dose-fractionation regimen has been debated for decades, ranging from single- to multifraction delivery using a range of regimens. Studies have also sought to evaluate the role of dose escalation using IMRT or SBRT as compared with conventional palliative RT doses and techniques.[10,74-79] In general, inclusion criteria for RCTs comparing various RT doses and techniques have been broad and overlapping between studies, and most RCTs did not provide statistical analyses for the differential effectiveness of interventions based on patient and disease characteristics. In addition to limiting conclusions regarding appropriate patient selection, this also hindered the ability to comment on how specific RT regimens may have interacted with factors known to be associated with disparities in health access, use, and outcomes. As such, the following factors to guide decision making are suggested when considering selection of regimens with higher biological effective dose (BED), advanced planning techniques, or both: better estimated prognosis, radioresistant tumor type, limited metastatic disease, receipt of prior RT, and ability to delay treatment to afford time for advanced planning when appropriate.[80] As described in KQ1, the primary outcome reported for most RCTs was pain response. Heterogeneity in both the definitions used as well as in the timing of assessment of this outcome impaired direct comparisons across studies.

Conventional palliative RT fractionation

Multiple RCTs evaluated the most effective single-fraction dose of palliative RT. The consensus of these studies determined that 800 cGy in 1 fraction was superior to other single-fraction dose regimens (eg, 400 cGy).[71,72] Similarly, more than 10 RCTs set out to determine the most effective multifraction regimen, with regimens of 2000 cGy in 5 fractions and 3000 cGy in 10 fractions among the most commonly used.[13,21,22,70,81,82]

To further understand the effects of fractionation on palliation of painful bone metastases, there have been many RCTs and nonrandomized studies comparing single- versus multifraction regimens of RT. Most of these studies included spine and nonspine metastases and many included metastases from a variety of malignant tumors; most were limited to "uncomplicated" bone metastases without existing or impending fracture, spinal cord or cauda equina compression, or history of prior RT. Almost all the studies used 800 cGy for the single-fraction arm. Conversely, there were a variety of multifraction regimens used throughout these studies. The most common regimens were 2000 cGy in 5 fractions and 3000 cGy in 10 fractions. Other multifraction regimens that were used include 2250 cGy in 5 fractions, 4000 cGy in 20 fractions, and 2400 cGy in 6 fractions.[11,24,30] The recommendation of multifraction regimens of 2000 cGy in 5 fractions and 3000 cGy in 10 fractions is based on the breadth of studies using these fractionation regimens.[11-13,20,24-29,31,70] The regimen 2400 cGy in 6 fractions is additionally included given that it was tested as part of the largest (n = 1171) multisite RCT of single versus multifraction RT.[11] Although the rates for overall pain response tended to be slightly lower at 4 weeks for single-fraction regimens as compared with multifraction regimens (ranging from 49% to 83% vs 53% to 89%, respectively, across 9 RCTs),[16,20,24-30] after 4 weeks of treatment, there was no statistically significant difference in pain reduction when comparing the single-fraction arm with the multifraction arm.[11,12,20,26,28,30,31] Shorter fractionation regimens (eg, 800 cGy in 1 fraction) are preferred given equivalence in pain outcomes. Despite lack of